Remarks:

Claims 1 to 15, 17 to 26, and 28 to 30 are pending.

Claim 1 has been amended to correct a typographical error.

No new matter is added.

Claims 1, 21, and 28 and their dependent claims are rejected under 35 USC 103(a) as obvious having regard to Tibshirani in view of Nguyen, and two or more other cited references. The Applicant respectfully traverses these rejections for at least the following reasons.

Claim 1 recites "collecting [...] a plurality of sets of data" and weights each "associated with, and indicating a statistical significance of" a collected set of data. Claim 1 also recites that each collected set of data is "associated with one member of said population" and comprises "non-genetic data, genetic data, and an indicator of disease status of said one member associated with said set."

As submitted in the last response, Tibshirani fails to disclose or suggest weights as recited in claim 1. The Examiner states that "Tibshirani teaches optimizing model parameters by calculating deviations in data sets using seventeen variables and using full, stepwise, and Lasso models (i.e., which incorporate minimized weighted values as described in Section 2) for data simulations (p. 390, Table I, p. 391, Section 5.2, Fig. 2))." However, the Examiner has not pointed to any specific disclosure in Tibshirani, or any other cited reference, for disclosing or suggesting weights each associated with an individual collected set of data as recited in claim 1. A skilled person would not understand Tibshirani as disclosing or suggesting such weights because it would be understood that the parameters $\boldsymbol{\beta}$ are associated with "variables" $\boldsymbol{X}$, not weights associated individual collected sets of data, as discussed in the last response. The specific sections and Table I and Fig. 2 of Tibshirani identified by the Examiner do not even state or show the expression "weight" and do not discuss weighing any collected

sets of data. Thus, the Examiner has failed to establish that this recited element is disclosed or suggested in Tibshirani, or any of the other recited references.

For this reason alone, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness of claim 1, as the recited references, either alone or in combination fail to disclose or suggest all of the elements recited in claim 1.

In addition, the Examiner admits that "Tibshirani does not specifically teach calculating weights determined with a constraint that weights are associated with sets of data having like genetic data are the same, as in claims 1, 2, 3, 19, 20, 21, and 28-30", but asserts that "Nguyen teaches calculating weights that associated with genetic data and subjected to a constraint that the weights all are equivalent with respect to orthogonality, as in claims 1, 21, and 28, which shows that weights associated with genetic data are the same" (emphasis added) and that it would have been obvious "to modify the statistical model of Tibshirani by calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same [...] since Nguyen teaches calculating weights that are associated with a linear combination of genes (i.e., like genetic data) and are subjected to the constraint that the weights are equivalent with respect to orthogonality, which shows weights associated with genetic data that are the same [...]" (emphasis added). The applicant respectfully disagrees for at least the following reasons.

For clarity, the entirety of the portion of Nguyen discussing the orthogonality constraint (Nguyen, at page 1626, col. 2, paragraph 3, line 12 from the bottom) is reproduced below:

> "The objective criterion for constructing components in PLS is to sequentially maximize the covariance between the response variable (**y**), survival time, and a linear combination of the genes (**X**). That is, in PLS, the components are constructed to maximize the objective criterion based on the sample covariance between **y** and a linear combination of **X**. Thus, we find the weight vector **w** satisfying the following objective criterion,
>
> $$\mathbf{w}_k = \text{argmax } \text{cov}^2 (\mathbf{Xw}, \mathbf{y}) \qquad (1)$$

$$\mathbf{w'w} = 1$$

subject to the orthogonality constraint

$$\mathbf{w'}_k\mathbf{S}\mathbf{w}_j = 0 \qquad \text{for all} \quad 1 \le j < k \qquad (2)$$

where $\mathbf{S} = \mathbf{X'X}$. The *ith* PLS component is also a linear combinations [*sc*] of the original genes, namely $\mathbf{t}_i = \mathbf{X}\mathbf{w}_i$, but the weights are non-linear functions of both **y** and **X**."

[emphasis added]

Nowhere in this quoted portion, or elsewhere in Nguyen, is it stated that "the weights all are equivalent with respect to orthogonality" and shown that weights associated with genetic data are the same," as alleged by the Examiner. The above quoted text merely states that the weights are subject to an orthogonality constraint and are non-linear functions of both **y** and **X**, where **y** is a variable representing survival time and **X** represents the genes. It is clear that each weight $\mathbf{w}_i$ is associated with a PLS (partial least square) component. However, there is no disclosure or suggestion that any weight in $\mathbf{w}_i$ is associated with an individual set of data that is associated with a member of the population, as recited in claim 1. In fact, it is clear from the expression "$\mathbf{t}_i = \mathbf{X}\mathbf{w}_i$" that the same weight vector $\mathbf{w}_i$ is applied to the gene matrix **X** to weigh individual gene matrix elements, regardless of the actual data values at the respective gene elements. Thus, $\mathbf{w}_i$ is not associated with any individual sets of data as recited in claim 1. A person skilled in the art would also understand that the orthogonality constraint disclosed in Nguyen does not require that the weights are the same for like genetic data. In fact, as each weight is a function of both **y** and **X**, the person skilled in the art would understand that the weight can vary depending on the values of survival time (**y**) even if the genes (**X**) have the same values.

Further, the Examiner seems to equate a constraint requiring that "weights associated with genetic data are the same" with a constraint requiring that "weights associated with sets of data having like genetic data are the same", without providing any rationale why this is considered so. The Applicant respectfully submits that these two constraints are substantively different and the former does not render the latter obvious. Thus, the disclosure of a constraint requiring that weights associated with genetic data are the same, even if were present in Nguyen, is not sufficient to show that

there is disclosure or suggestion of a constraint requiring that weights associated with sets of data having like genetic data are the same.

The distinction between "genetic data" in general and "sets of data having like genetic data" is significant in the context of claim 1. As recited in claim 1, each data set includes a combination of genetic data and non-genetic data, and the weights are determined with a constraint that weights associated with sets of data having like genetic data are the same, regardless of the values of non-genetic data in the same data sets. The Examiner has not indicated where in the cited references it is disclosed or suggested that when genetic data and non-genetic data are combined to calculate disease risks, the weights associated with the combined data sets should be determined with a constraint as recited in claim 1 of the present application. It is respectfully submitted that there is no disclosure, suggestion, or motivation provided in either Tibshirani or Nguyen, or any other cited references, either alone or in combination, that the two types of data (genetic and non-genetic) should be used in combination as recited in the claims of the present application.

Thus, it is respectfully submitted that the Examiner has also failed to establish that Nguyen discloses or suggests the feature of "calculating weights determined with a constraint that weights associated with sets of data having like genetic data are the same", in combination with other features recited in claim 1.

Review of other cited references reveals that they fail to cure the defects of Tibshirani and Nguyen discussed above.

Claim 1 also recites optimizing the parameters of the candidate model by fitting, wherein the fitting comprises "calculating for each of said sets, a deviate of a predicted risk from an indicator of disease status for that set, said predicted risk predicted using said candidate model and non-genetic data in that set." There is no disclosure or suggestion in the cited references, either alone or in combination, that when the predicted risks are calculated using a prediction model and non-genetic data, the deviates of the predicted risks used in the fitting process are to be weighed by weights

determined with a constraint based on genetic data, as recited in claim 1 of the present application. The Examiner has failed to point to any specific disclosure in the cited art for disclosing or suggesting these recited features, or explain why the combination of these features as recited is obvious.

It is submitted that the subject matter of claim 1 patentably distinguishes over the prior art, not merely because the weights are determined as recited, but also because the weights so determined are used in the fitting process to optimize the parameters of a candidate model that is in turn used, in combination with non-genetic data in the collected data sets, to calculate predicted risks, as recited in claim 1. The Examiner has not provided any rationale for why it is considered obvious to modify Tibshirani, Nguyen, and the other cited references, to arrive at these recited features in combination, and the Applicant respectfully submits that there is none disclosed or suggested in the cited references.

Likewise, it is submitted that claim 21, and claims dependent directly or indirectly from claim 1 or claim 21 are also patentably distinguishable over the cited references, for the same reasons.

Claim 28 recites assessing "a goodness of fit of data derived from a plurality of members of said population, said assessing comprising calculating a deviate from an indicator of a disease status of each member by a predicted risk for that member, predicted using that model and non-genetic data associated with that member, and a sum of weighted deviates, each deviate weighted by a weight reflecting genetic data associated with that member for whom that deviate is calculated" (emphasis added).

For similar reasons as discussed above with reference to claim 1, it is respectfully submitted that the cited references either alone or in combination fail to disclose or suggest the combination of predicting risk for a member of a population using a statistical model and non-genetic data associated with that member, and weighing the deviate of the predicted risk from an indicator of disease status of that member by a weight reflecting genetic data associated with that member, in combination

with other features recited in claim 28. The Examiner has failed to point to any specific disclosure in the cited reference for disclosing or suggesting weights each associated with an individual member of a population and reflecting genetic data associated with that member, in combination with weighing deviates for predicted risks where the predicted risk for a member is predicted using non-genetic data associated with that member. As this feature is not disclosed or suggested in the cited references, the Examiner has failed to establish a *prima facie* case of obviousness for claim 28.

Thus, withdrawal of the rejections to independent claims 1, 21, and 28, and claims dependent therefrom, is respectfully requested.

In view of the foregoing, favourable consideration of the application is respectfully requested.

Respectfully submitted,

DINSMORE & SHOHL, LLP

By: /John D. Reed/
John D. Reed
Registration No. 46,506

One Dayton Centre
One South Main Street
Suite 1300
Dayton, OH 45402

Tel.: (937) 449-6400
Fax: (937) 449-6405

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